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Neurotoxicity Testing of Agricultural Workers Exposed to Pesticides

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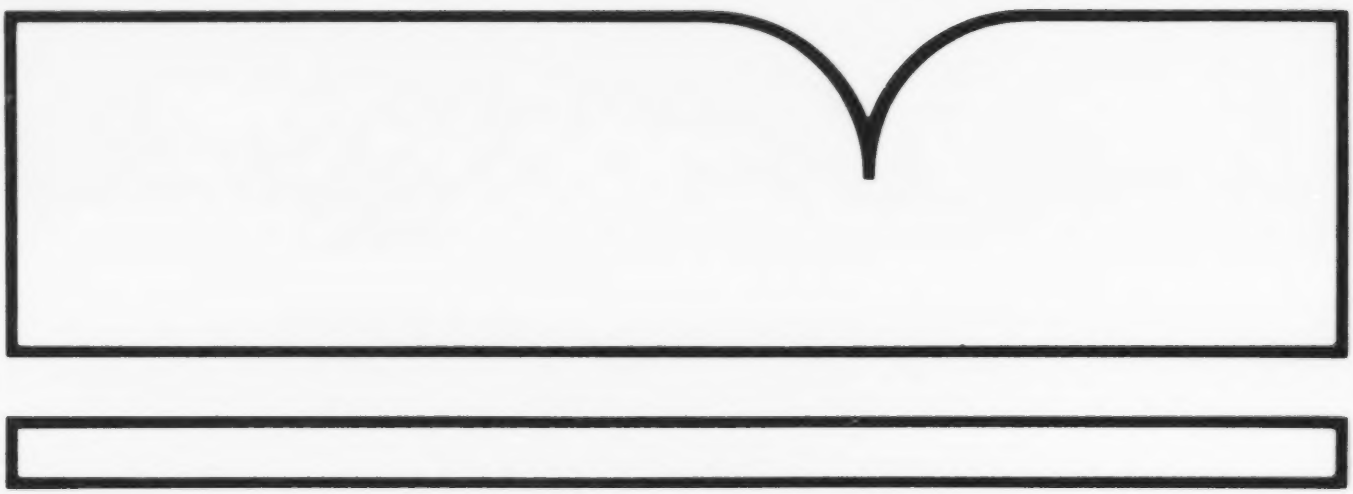

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NEUROTOXICITY TESTING OF AGRICULTURAL WORKERS EXPOSED TO PESTICIDES

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16. ABSTRACT

The farmer has been one of the major beneficiaries of the chemical revolution that has occurred over the past half century. The develoment of new fertilizers, pesticides, herbicides, fungicides and other agricultural chemicals has dramatically increased crop yields and reduced crop losses due to insects and disease. Agrochemicals, however, frequently have hidden costs that may not become apparent for years after they have been introduced on the maket. Hazards to human health in the form of acute and delayed neurotoxicity resulting from pesticide exposure are the hidden costs that will be addressed in this paper.

Anger (1) recently pointed out that direct nervous system effects have been used as one of the bases of exposure standards for 167 of the 558 industrial chemicals for which "safe" exposure standards have been recommended. Although the discipline of neurobehavorial toxicology has grown steadily during the past decade, it is still an infant discipline within the larger field of toxicology. The first challenge therefore, is to highlight the relevance of neurobehavorial toxicology in the health assessment of agricultural workers. A brief review of the acute and delayed neurotoxicity of organophosphorus pesticides will be used to focus attention on the importance of neurobehaviroal evaluations. Specific testing methods appropriate for the health assessment of agricultural workers will then be reviewed.

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The farmer has been one of the major beneficiaries of the chemical revolution that has occurred over the past half century. The development of new fertilizers, pesticides, herbicides, fungicides and other agricultural chemicals has dramatically increased crop yields and reduced crop losses due to insects and disease. Agrochemicals, however, frequently have hidden costs that may not become apparent for years after they have been introduced on the market. Hazards to human health in the form of acute and delayed neurotoxicity resulting from pesticide exposure are the hidden costs that will be addressed in this paper.

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ACUTE NEUROTOXICITY OF ORGANOPHOSPHORUS PESTICIDES

Organophosphorus (OP) pesticides are widely used today in agriculture. Exposure to OP pesticides can produce acute cholinergic symptoms in humans as well as insects that the compounds are designed to eradicate. Table 1 summarizes the characteristic signs and symptoms of acute OP pesticide poisoning and indicates the sites affected in the peripheral and central nervous systems. A bewildering variety of parasympathetic, autonomic and sympathetic nervous functions are affected. All of these symptoms, however, are directly attributable to a single mechanism of action of OP pesticides on neural transmission. These are acute symptoms produced by the inhibition of acetylcholinesterase (AChE) at cholinergic synapses in the nervous system (2). AChE is an enzyme that breaks down the neural transmitter acetylcholine. The post-synaptic accumulation of acetylcholine causes an initial increase in firing and then paralysis of neural transmission at cholinergic synapses. Disruption of muscarinic receptors in the parasympathetic nervous system affects the exocrine glands; gastrointestinal, respiratory and cardiovascular systems; and the bladder. Disruption of nicotinic receptors in somatic motor nerves affects the skeletal muscles, and disruption of acetylcholine receptors in the central nervous system affects arousal, cognitive processes, and breathing. The wide range of symptoms can thus be reduced to the inhibition of AChE at cholinergic synapses throughout the nervous system.

ORGANOPHOSPHOROUS INDUCED DELAYED NEUROTOXICITY (OPIDN)

In addition to the acute cholinergic effects described above, some organophosphorous esters produce a different and devastating nervous system syndrome called "organophosphorous induced delayed neurotoxicity" or OPIDN (3,4). The classical OPIDN syndrome entails progressive weakness and ataxia

leading in severe cases to flaccid paralysis. The symptoms begin distally in the lower limbs and may spread to the spinal cord and upper limbs. Although peripheral nerve damage may recover slowly, spinal cord degeneration is likely to produce irreversible spasticity, ataxia, or quadriplegia. The extent of involvement and severity of symptoms depend on the specific compound as well as the length and intensity of exposure.

The cardinal features of OPIDN include: (a) a characteristic delay in the onset of clinical symptoms (6-21 days after exposure); (b) a marked species difference in sensitivity (cats, horses, sheep, birds, and humans are very susceptible, while rodents and rabbits are not); and (c) a stereotypic morphological pattern of action (Wallerian or dying-back axonopathy of distal nerves with progressive degeneration back toward the cell body).

There is little correlation between the acute cholinergic and delayed neurotoxic effects of OP pesticides. That is, the acute toxicity of a particular compound as measured by AChE inhibition is of little value in predicting the occurrence of OPIDN (3). OP pesticides that have been reported (2,4) to induce delayed neurotoxicity include leptophos, fenthion, isofenphos, EPN, trichlorfon, and methamidiphos. In the cases of leptophos and fenthion, human neurological symptoms were the first indicators of trouble. Workers in the plant where leptophos was being manufactured experienced a variety of puzzling symptoms that were initially diagnosed as multiple sclerosis. In the course of a NIOSH health hazard evaluation in 1976 (5), the OPIDN syndrome was discovered, and the pesticide was subsequently withdrawn from the U.S. market. The use of leptophos was terminated in Egypt for a different reason: extensive application in the Nile delta resulted in the paralysis and death of 1300 water buffalo (6).

Fenthion is an OP compound that is used as a fumigant, fungicide, and dermal pesticide in large animals (7). Sensory polyneuropathies have been reported in veterinary workers who regularly used a fenthion solution to rid small animals of fleas (3). Symptoms of ataxia and paresthesias evolved slowly over a two year period in these workers.

Both fenthion and leptophos were approved for production and application in agriculture before discovering the serious human health hazard of delayed neurotoxicity associated with these compounds. Are these isolated cases, or is there a more pervasive hazard among the hundreds of organophosphorus pesticides currently used in agriculture? Neurobehavioral monitoring of agricultural workers chronically exposed to OP pesticides would be prudent to prevent further unexpected incidents of acute or delayed neurotoxicity.

NEUROTOXICITY TESTING METHODS

A brief overview of neurobehavioral testing methods appropriate for health assessment will now be presented. Neurotoxicity testing methods will be broken down into three general categories -- psychomotor, psychophysical and electrophysiological. The psychomotor category includes traditional behavioral tests of sensorimotor integration, motor coordination, and memory. The psychophysical category includes tests of auditory, visual, and tactile sensitivity, and the electrophysiological category includes sensory measures derived from scalp or dermal-recorded electrical activity of the brain or peripheral nerves. The tests to be reviewed are appropriate for the evaluation of the range of neurobehavioral symptoms associated with pesticide poisoning in humans and many are recommended by the World Health Organization (8).

A. Psychomotor Test Batteries

Table 2 lists neurobehavioral tests recommended by the World Health Organization (8) for neurotoxicity testing in the workplace. The functional nature of each test, a minimal or "core" screening battery, and additional or alternative tests for in-depth assessments are specified. The selection of these tests was based on results of occupational health studies during the past two decades. Each of the tests is standardized, validated, reliable and has been shown to be sensitive in workers to the effects of toxicant exposure. The digit symbol, digit span, and block design subscales of the Wechsler Adult Intelligence Scale, in particular, have proven to be sensitive to a wide variety of chemicals (9). The Santa Ana Dexterity Test has also proven to be a very sensitive test of occupational exposure (9). This test is simple and rapid to administer, but is not available commercially.* The WHO core battery would be appropriate for screening agricultural workers exposed to pesticides.

B. Psychophysical Tests

Psychophysical testing has long been used in worker monitoring programs in the form of audiometric assessment. Psychophysical tests of tactile sensitivity and thermal sensitivity have recently been developed specifically for occupational assessment (10). The loss of tactile sensitivity is one of the earliest signs of peripheral neuropathy, a condition that can result from diabetes, carpal tunnel syndrome, chronic alcoholism, or exposure to a variety of chemicals including organophosphorus pesticides (11). A simple and inexpensive device for quantitative tactile testing that could

*This test may be obtained from the Division of Biomedical and Behavioral Science, National Institute for Occupational Safety & Health, 4676 Columbia Pkwy, Cincinnati, OH 45226 USA

be used for field testing or monitoring of agricultural workers is available from Sensortek Inc (Clifton, NJ 01013 USA).

Tactile sensation is a good metric of neurotoxicity because large-diameter axons that conduct vibratory information are susceptible to damage from chemicals such as acrylamide, lead and alcohol (11,12). In some cases small fibers that conduct pain and temperature sensation are affected before large fibers. Traditional clinical and electrophysiological tests such as nerve conduction velocity are relatively insensitive to small, slower-conducting nerve fibers (13). Quantitative assessment of thermal sensation, therefore, offers a useful adjunct for clinical neurological as well as neurotoxicological evaluations. A thermal sensitivity tester is also available from Sensortek for neurological and occupational screening.

The visual system is also unusually vulnerable to chemical exposure (14). Simple assessment of visual acuity with a Snellen eye chart is useful in neurotoxicity screening, although more sensitive and sophisticated tests are available. Contrast sensitivity testing (15) is a new procedure to evaluate the ability of the eye to discriminate spatial frequencies. Contrast sensitivity is altered by macular disease, lesions of the optic tract, and glaucoma (15). The potential utility of contrast sensitivity methods in neurotoxicity testing has been demonstrated in the assessment of Minimata Disease [methyl mercury poisoning] (16).

C. Electrophysiological Testing Procedures.

The final methodology to be considered derives from dermal or scalp recordings of electrical activity in the central and peripheral nervous system. Motor and sensory nerve conduction velocity (NCV) measures are basic tools in clinical neurology and are the most widely used electrophysiological measures in human neurotoxicity testing. In the case of lead

exposure which can produce demyelinating lesions and peripheral neuropathy in adults, NCV measures provide a useful and sensitive method for monitoring and evaluating exposed workers (17). Demyelinating lesions clearly slow nerve conduction. If toxicant exposure produces selective axonal degeneration, however, NCV measures are unlikely to show any demonstrable early effect (13). As long as a portion of the nerve fiber is intact, NCV may be normal. The amplitude of the action potential remains within normal limits until more than 50% of the fibers in a given nerve cease to function (13). In the case of the distal axonopathy characteristic of OPIDN, NCV measures would be unlikely to show any effect until irreversible damage was done. Tactile or thermal sensitivity testing should provide a more sensitive and useful early sign of organophosphorus-induced delayed neuropathy.

Sensory evoked potential (EP) tests may also be useful for neurotoxicity assessment (12,18). The development and clinical application of sensory EP tests has proceeded rapidly in parallel with advances in microprocessor technology during the past decade. Sensory EPs are now used widely in neurology, audiology, and ophthalmology as adjuncts to traditional clinical examinations. Sensory EPs provide noninvasive, objective, and reliable measures of the functional integrity of auditory, visual, and somatosensory pathways from peripheral receptors to cortical projection areas. The measures are useful in detecting and in some cases localizing lesions in sensory pathways. These measures have also become routine diagnostic tools in the assessment of nonspecific demyelinating diseases such as multiple sclerosis (19). For these reasons sensory EPs are very promising candidates for neurotoxicity testing, although surprisingly little human data are presently available to test this assumption. Sensory EPs have been used extensively in animal models (20) to characterize the neurotoxicity of a wide range of chemicals.

The remarkable comparability of sensory EPs in species as disparate as rat and man also contributes to the utility in neurotoxicology of these measures for cross-species extrapolation.

Concluding Comments

A brief overview of the neurotoxicity of organophosphorus pesticides and appropriate methods for testing exposed workers has been presented. The insidious, delayed effect of exposure to organophosphorus pesticides, initially considered to pose no hazard to humans at low concentrations, is an important concern for agricultural workers. Incidents in which exposure to leptophos and fenthion resulted in the unexpected development of delayed peripheral neuropathies were reviewed. The effects of chronic low level exposure to pesticides have not been adequately studied. The marked species specificity of OPIDN underscores the need to study the consequences of chronic exposure in agricultural workers.

Improved health monitoring programs are needed in rural areas for early detection of subclinical effects of pesticide exposure. Appropriate remedial steps can often be taken before irreversible damage has been done. By the time clearcut clinical symptoms of OPIDN appear, the damage is often irreversible. The earliest complaints expressed by workers exposed to pesticides are frequently neurobehavioral signs such as headache, excessive fatigue, numbness of extremities, visual disturbances or emotional signs such as increased irritability, anxiety and depression. Awareness of these symptoms as early signs of pesticide poisoning is crucial among health care professionals in agricultural communities.

Several of the measures described above -- vibratory, thermal, and contrast sensitivity testing, in particular -- are well suited to worker screening and monitoring programs. The psychomotor and psychophysical

testing procedures are simple to administer and score, require little time to perform, are light-weight and portable for use in field studies, and have proven to be sensitive to occupational and environmental toxicants. Wider application of neurobehavioral tests in agricultural health research, screening and monitoring could significantly reduce the health risks of pesticide exposure in the agricultural community.

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TABLE 1. SIGNS AND SYMPTOMS OF ORGANOPHOSPHORUS PESTICIDE POISONING*

A. Parasympathetic Autonomic Nervous System (Muscarinic Receptors)

Site Affected	Manifestations
Exocrine glands	Increased salivation, lacrimation, perspiration
Eyes	Miosis (pinpoint and nonreactive), ptosis, blurring of vision, conjunctival injection, "bloody tears"
Gastrointestinal tract	Nausea, vomiting, abdominal tightness, swelling and cramps, diarrhea, tenemus, fecal incontinence
Respiratory tract	Excessive bronchial secretions, rhinorhea, wheezing, edema, tightness in chest, bronchospasms, bronchoconstriction, cough, bradypnea, dyspnea
Cardiovascular system	Bradycardia, decrease in blood pressure
Bladder	Urinary frequency and incontinence

B. Somatic Motor Nerve Fibers (Nicotinic Receptors)

Skeletal muscles	Muscle fasciculations (eyelids, fine facial muscles), cramps, diminished tendon reflexes, generalized muscle weakness in peripheral and respiratory muscles, paralysis, flaccid or rigid tone
	Restlessness, generalized motor activity, hyperreactivity to acoustic stimuli, tremulousness, emotional liability, ataxia

C. Central Nervous System (Acetylcholine Receptors)

Midbrain, cortex	Drowsiness, lethargy, fatigue, mental confusion, inability to concentrate, headache, pressure in head, generalized weakness
	Coma with absence of reflexes, tremors, Cheyne-Stokes respiration, dyslpnea, convulsions, depression of respiratory centers, cyanosis

*Adapted from Echobichon & Joy (2), p.166.

Table 2.—Proposed Psychological Test Methods*

Functional Domain	Screening Battery Minimum Program	Additional and Alternative Methods for a Standard Battery	Tests for In-Depth Studies or Tests to be Developed Further
Motor speed	Finger Tapping		Two-plate tapping
Motor steadiness	Flanagan Coordination or Mira	Aiming Tremometer	Body steadiness
Reaction time		SRT (60–100 signals) CRT	Series of RT-tasks with increasing complexity
Perceptual-motor speed	Digit Symbol, WAIS	Bourdon-Wiersma Neisser Identical Numbers	Combinations of different perceptual-motor speed test
Motor coordination	Santa Ana or some other dexterity test	Michigan Eye-Hand Coordination Purdue Pegbord	Other psychomotor tests
Visual cognitive functions	Visual Retention, WMS	Block Design, WAIS Embedded Figures Benton Visual Retention Symmetric Drawing	Picture completion, WAIS Object assembly (WAIS) Figure classification Memory-for-Design Test
Verbal abilities	Digit Span, WAIS, WMS Logical Memory, WMS Similarities, WAIS	Associative Learning, WMS Stroop Color Naming Test	Various memory span tests Memory tests with delayed recall Tests for auditory and semantic processing Verbal comprehension tests
Attention/vigilance		PASAT (Paced Auditory Serial Attention Test) Continuous Performance Test	Audiovisual Vigilance Test Other tests for attention and vigilance
Moods, emotions	POMS (Profile of Mood States)	Taylor Manifest Anxiety Scale EPI (Eysenck Personality Inventory)	Rorschach

* Presented at WHO International Meeting on the Prevention of Neurotoxic Illness in Working Population, meeting at NIOSH, Cincinati, Ohio, May, 1983